stringent statistical test (a two-tailed Dunnett's test). However, based on other statistical analyses used in the field-the single- and two-tailed student's T statistical analysis–this increase would be deemed statistically significant. (Tr. at 736:11-23, 738:7-740:9 (McOsker Dir.); Tr. at 854:20-856:12, 856:21-857:8, 861:10-863:3 (Miller Dir.); PTX 22 at PG23092, PG23101; P-39).

321. Thus, the testing of risedronate in the Schenk assay confirmed that risedronate had an LED of 0.0003 mg P/kg/day. (Tr. at 732:15-24 (McOsker Dir.)).

322. P&G conducted the TPTX and Schenk assays in an appropriate manner consistent with the standard techniques and best practices in use in the mid-1980s. (Tr. at 864:18-23 (Miller Dir.)).

323. P&G's determination based on the Schenk assay and the TPTX assay that risedronate had an LED of 0.0003 mg P/kg/day was proper. (Tr. at 853:10-854:19, 858:9-13 (Miller Dir.); PTX 22; PTX 141; PTX 514; PTX 519.)

324. PTX 139 is a biweekly report written by Kent Buckingham dated October 4, 1985, summarizing the results of testing for risedronate (3-pyr EHDP) and 3-pyr PHDP. (Tr. at 474:11-14; 475:1-2 (Benedict Dir.); PTX 139).

325. Dr. Benedict received a copy of PTX 139 at the time it was written. It was Mr. Buckingham's ordinary course to report on the results of research in his group, and Dr. Benedict received such results in the ordinary course of business. (Tr. at 474:7-24 (Benedict Dir.); PTX 139).

326. In PTX 139, Mr. Buckingham wrote: "Ms. J.E. McOsker determined an actual lowest effective dose (LED) for 3-pyr HEDP by evaluating a range of dose levels below those initially screened (0.1, 0.01, 0.001 and 0.0003 milligrams of phosphorus per

kilogram)." (Tr. at 475:3-11 (Benedict Dir.); PTX 139). In this sentence, Mr. Buckingham is referring to the TPTX results on risedronate (3-pyr EHDP). (Tr. at 475:14-476:1 (Benedict Dir.); PTX 139).

d. Differences in Efficacy Between Risedronate and Related Compounds

327. The 2-pyr EHDP compound was also tested using both the TPTX assay and the Schenk assay. *See* PTX 516; PTX 518.

328. PTX 516 is Karen Johnson's lab notebook reflecting TPTX testing conducted on 2-pyr EHDP by Ms. Johnson. Such lab notebooks were maintained by P&G in the ordinary course of business. (Tr. 740:20-741:22 (McOsker Direct); Tr. 443:4-14 (Benedict Direct).)

329. PTX 518 is John Bevan's lab notebook reflecting Schenk testing conducted on 2-pyr EHDP. Such lab notebooks were maintained by P&G in the ordinary course of business. (Tr. 741:23-743:4 (McOsker Direct); Tr. 443:4-14 (Benedict Direct).)

330. Karen Johnson conducted the TPTX test of 2-pyr EHDP. (PTX 109; PTX 518.) Ms. Johnson ran TPTX assays at P&G for a year or more. (Tr. at 491:22-492:3 (Benedict Cross)).

331. PTX 109 is a proposal to begin development of 2-pyr EHDP dated April 8, 1985 from Dr. Benedict's group that reflects Ms. Johnson's assessment of 2-pyr EHDP in the TPTX model. (Tr. 458:15-459:12 (Benedict Direct).

332. P&G tested 2-pyr EHDP in the TPTX assay at doses of 1.0, 0.10, 0.01, and 0.001 mg P/kg/day. PTX 516 at PG 191357. The TPTX assay indicated that 2-pyr EHDP had an LED of 0.001. PTX 109.

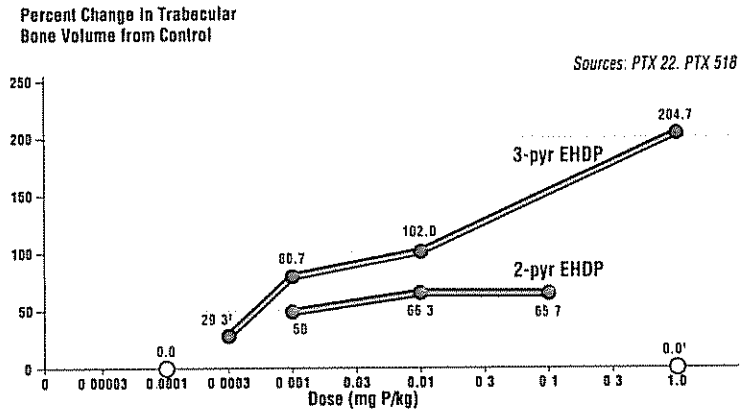
333. Subsequently, John Bevan tested 2-pyr EHDP in the Schenk assay at doses of 10, 1.0 0.1, 0.01, 0.001, and 0.0001 mg P/kg/day. (Tr. at 743:5-13 (McOsker Dir.); PTX 507; PTX 518 at PG 191440). Based on a histological analysis, this assay confirmed that 2-pyr EHDP had an LED of 0.001. (PTX 148 at 78488; Tr. at 805:10-11 (Miller Cross).)

334. PTX 507 is a biweekly report dated May 22, 1985 written by James Powell discussing study of modified 2-pyridyl compounds, indicating that Mr. Bevan conducted Schenk testing of 2-pyr EHDP. Such reports were prepared and distributed in the ordinary course of business at P&G. (Tr. 459:21-460:20 (Benedict Dir.).)

335. At the two highest doses, 10 and 1.0 mg P/kg/day, 2-pyr EHDP killed all of the test animals. (Tr. at 743:14-19 (McOsker Dir.); PTX 518 at PG 191444). This fact was particularly significant given that the 1.0 mg dose was considered an effective dose for etidronate and chlodronate, two of the prior art bisphosphonate compounds over which researchers were trying to improve at that time. (Tr. at 743:20-744:4 (McOsker Dir.)).

336. Risedronate was also tested at the 1.0 mg P/kg dose, and it showed more than a 200% increase in bone volume at that dose. (Tr. at 743:20-744:4 (McOsker Dir.); Tr. at 751:5-752:23 (McOsker Cross); Tr. at 863:4-864:9 (Miller Dir.); PTX 22 at PG 23101; P-39).

337. The picture below illustrates the difference in efficacy between 2-pyr EHDP and risedronate in the Schenk assay based upon histological analysis:



(Tr. at 859:19-864:9 (Miller Dir.); P-39).

338. It was unnecessary to test risedronate and 2-pyr EHDP at all of the same doses to make a comparison of the compounds. (Tr. at 864:10-17 (Miller Dir.)).

339. The potency of 2-pyr EHDP is substantially lower than and inferior to that of risedronate. (Tr. at 859:11-864:9 (Miller Dir.); P-39).

340. P&G tested the efficacy of 4-pyr EHDP. The results of that testing showed that 4-pyr EHDP was "a dud"-it was approximately 100 times less potent than 3-pyr EHDP. (Tr. at 481:19-482:10 (Benedict Dir.); PTX 148 at PG 78490).

341. PTX 148 is a series of efficacy and toxicity data sheets for various compounds prepared by Dr. Eastman. Dr. Eastman prepared these summaries in the ordinary course of his business at P&G, and P&G maintained these documents in the ordinary course of business by P&G. (Tr. 785:22-787:4 (Eastman Dir.).)

342. Risedronate was 30 times more potent than the pyr-EDP compounds, 100 times more potent than 4-pyr EHDP, and three times more potent than 2-pyr EHDP. (Tr. at 476:8-18, 481:19-482:10 (Benedict Dir.)).

343. Dr. Benedict would not have been able to predict these differences in potency before synthesizing and testing these compounds. (Tr. at 476:8-18 (Benedict Dir.)).

2. Toxicity Screening

344. Many drugs have good potency but are nonetheless not advanced because they are unsafe. (Tr. at 839:20-840:3 (Miller Dir.)).

345. Shorter-term toxicity screening provides information that may be used to elucidate a compound's primary toxicity and to look at compounds relative to one another. Specifically, shorter-term toxicity screening may be used to determine the highest dose of a compound that can be administered without causing toxic effects and to rank the compounds against one another on that basis. (Tr. at 772:6-13 (Eastman Dir.); Tr. at 851:2-20 (Miller Dir.)).

346. Short-term toxicity screening differs in scope and purpose from longer-term toxicity testing. Longer-term studies are designed to support safety testing for Investigational New Drug applications ("INDs") to the FDA. Such studies require a larger amount of compound under study, as well as large amounts of time and money. (Tr. at 771:15-772:5 (Eastman Dir.)).

347. In the mid-1980s, P&G developed a short-term toxicity screen protocol to look at a large number of compounds in a manner that was reliable, predictive of test compound potential, and cost-effective, such that promising compounds could be quickly identified and selected for further development. (Tr. at 770:12-771:14 (Eastman Dir.)).

348. PTX 82 is a report detailing the 2-day toxicity screening of risedronate written by Dr. Eastman. It was Dr. Eastman's usual practice to prepare such reports at

P&G, and P&G maintained these documents in the ordinary course of business. (Tr. 775:17 – 777:18 (Eastman Dir.); PTX 82.)

349. P&G used a two-day IV toxicity screen in which rats were dosed with a test compound intravenously on two consecutive days for fifteen minutes. At the end of two days, in-life observations and samples were taken from the rats. Then, they were sacrificed and necropsied. Various organ systems including the kidney, liver, stomach, urinary tract, were examined for signs of toxicity because they were known "organs of toxicity" with bisphosphonates. In addition, the liver and kidney are often targets of drug toxicity. (Tr. at 772:14-773:23 (Eastman Dir.); PTX 82 at PG 57089-90).

350. These tests and examinations were performed at P&G by a team consisting of technicians that do the in-life work, professionally trained or highly experienced clinical pathologists and anatomic pathologists, under the supervision of a study director or project director. Dr. Eastman was the study or project director who oversaw the toxicity screening program during the mid-1980s. He designed the protocol and was responsible for assembling the data and ensuring that the study had a clear and understandable message. (Tr. at 773:24-774:14 (Eastman Dir.)).

351. Dose levels for toxicity screening were selected in order to identify dose levels where the toxic effects of the drug could be observed–what organs they effect and how severe those effects are–and also to find the dose at which no such toxic effects would be observed, *i.e.*, the no observable effect level ("NOEL"). (Tr. at 774:15–775:2 (Eastman Dir.)).

352. The NOEL for a compound was the next dose below that at which any toxic effects were observed. (Tr. at 775:3-16 (Eastman Dir.)).

a. Toxicity Screening of Risedronate

353. Risedronate underwent toxicity screening from October 2-4, 1985. (Tr. at 779:18-780:4 (Eastman Dir.); PTX 82 at 57102).

354. Based on this toxicity screening, P&G properly concluded that the NOEL for risedronate was 0.75 mg P/kg/day. (Tr. at 777:19–778:6 (Eastman Dir.); Tr. at 865:6-866:14 (Miller Dir.); PTX 82 at PG 57087).

355. The basis for this determination was that at the next highest dose, 2.5 mg P/kg/day, P&G observed both renal and gastric toxicity and changes in the blood urea nitrogen ("BUN"), a measure indicative of kidney toxicity, and creatine. At the 0.75 mg P/kg/day dose, increased leukocyte (white blood cell) counts were observed. However, it was concluded that this increase was due to slight infection caused by the surgical procedures necessary to implant the intravenous device in the rats, and was not related to the drug itself. (Tr. at 778:7-779:17, 788:13-17 (Eastman Dir.)).

356. Dr. Eastman typically reported the results of such tests to the study team, which included Dr. Benedict, as soon as they were available, which would be within a few weeks of completion of the animal protocol. (Tr. at 779:18-780:10, 783:16-22 (Eastman Dir.); PTX 82 at PG 57102).

357. PTX 82 is the report summarizing the toxicity screening of risedronate. PTX 82 is an accurate summary of the two-day IV toxicity screen that was conducted on risedronate. (Tr. at 775:17-776:21 (Eastman Dir.); PTX 82).

358. It was Dr. Eastman's usual practice to prepare such reports in connection with the toxicity screening that he conducted, and such reports were maintained by P&G in the ordinary course of business. (Tr. at 777:2-18 (Eastman Dir.)).

b. Differences in Toxicity Between Risedronate and Other Related Compounds

359. Dr. Benedict received the results of the toxicity screen, which revealed that risedronate was "delightfully less toxic" than 2-pyr EHDP. (Tr. at 476:21-477:11 (Benedict Dir.)).

360. PTX 81 is a report detailing the 2-day toxicity screening of 2-pyr EHDP, which was directed and overseen by Dr. Eastman. It was Dr. Eastman's usual practice to prepare such reports at P&G, and P&G maintained these documents in the ordinary course of business. (Tr. 777:13-18, 780:11 – 781:9 (Eastman Dir.); PTX 81.)

361. Dr. Eastman also conducted the toxicity screening on 2-pyr EHDP, which took place from October 29, 1985 to November 1, 1985. (Tr. at 781:4-9, 782:22-783:7 (Eastman Dir.)).

362. Based upon this toxicity screening, P&G properly concluded that the NOEL for 2-pyr EHDP was 0.25 mg P/kg/day. (Tr. at 780:11-782:13 (Eastman Dir.); Tr. at 865:6-866:14 (Miller Dir.); PTX 81 at PG 57031).

363. The basis for this conclusion was that at two higher doses of 2-pyr EHDP, 0.75 mg P/kg/day and 2.5 mg P/kg/day, there were substantial toxic effects in the kidneys, liver, and stomach, including increases in serum enzyme from the liver, increases in the BUN and creatine, fatty change in the liver, and necrosis in the kidney. (Tr. at 781:22-782:21 (Eastman Dir.); PTX 81 at PG 57031).

364. In comparison to the renal and kidney toxicity that P&G observed for 2-pyr EHDP at the 0.75 dose, P&G saw no such toxicity for risedronate at that dose. (Tr. at 782:14-21 (Eastman Dir.); *compare* PTX 81 to PTX 82).

365. PTX 80 is a report detailing the 2-day toxicity screening of 4-pyr EHDP, which was directed and overseen by Dr. Eastman. It was Dr. Eastman's usual practice to prepare such reports at P&G, and P&G maintained these documents in the ordinary course of business. (Tr. 777:13-18, 783:23-784:14 (Eastman Dir.); PTX 80.)

366. Based on this toxicity screening, P&G properly concluded that the NOEL for 4-pyr EHDP was 0.75 mg P/kg/day. (Tr. at 783:23-785:14 (Eastman Dir.); Tr. at 865:6-866:14 (Miller Dir.); PTX 80 at PG 56965).

367. The basis for this conclusion was that at the higher dose of 4-pyr EHDP tested, P&G observed kidney toxicity, a change in body and kidney weight, and increases in enzyme levels indicative of liver toxicity. There were no such observations at the 0.75 dose. (Tr. at 785:4-14 (Eastman Dir.); PTX 80).

368. Slide P-36a is a slide prepared by Dr. Eastman that summarizes the various BUN results that P&G obtained for 2-pyr EHDP, risedronate, and 4-pyr EHDP. (Tr. at 789:18-792:5 (Eastman Dir.); P-36a).

369. Procter & Gamble conducted the two-day toxicity screening of 2-pyr EHDP, risedronate, and 4-pyr EHDP in an appropriate manner consistent with the standard techniques and best practices in use in the mid-1980s, and the data obtained from that screening is reliable. (Tr. at 866:15-867:9 (Miller Dir.)).

370. Before conducting the toxicity screening on 2-pyr EHDP, risedronate, and 4-pyr EHDP, Dr. Eastman and P&G had no expectation as to the relative toxicities of thee three compounds. (Tr. at 785:15-21 (Eastman Dir.)).

3. Evaluation of Efficacy and Toxicity Results

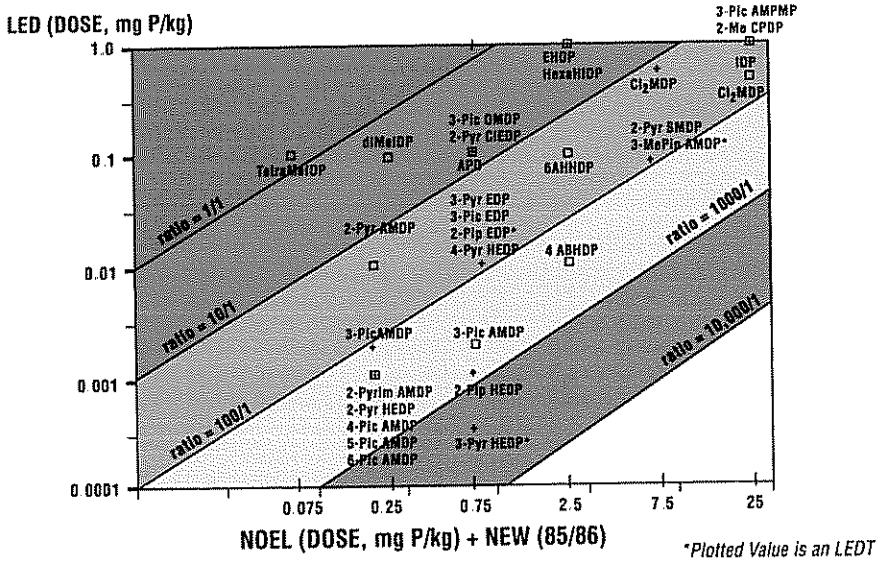
371. In order to evaluate compounds for potential further development, researchers create a ratio of the NOEL of a compound compared to the LED of that

compound, which is sometimes referred to as the therapeutic window or safety window. (Tr. at 851:21-852:3 (Miller Dir.)).

372. It is of great clinical importance to have as wide a safety margin as possible. The wider the margin of safety, the more flexibility exists within the dosing window for different kinds of therapeutic regimens, different doses, and different clinical applications. A wide safety margin also provides a greater margin of safety at the consumer level. (Tr. at 852:7-14 (Miller Dir.)).

373. PTX 148 is a summary of the data that P&G had accumulated concerning the results of the efficacy and toxicity screening of various bisphosphonates that P&G had performed at that time. With the exception of the cover memo from Mr. Buckingham, the summary data sheets were prepared by Dr. Eastman and maintained by P&G in the ordinary course of business. (Tr. at 785:22-787:4 (Eastman Dir.); PTX 148).

374. PTX 148 includes a graph that shows all of the compounds that P&G had screened for efficacy and toxicity and the relationship between LED and NOEL for each. Below is a version of this graph:



LED, based on either the TPTX assay or the Schenk assay, is plotted on the y-axis based on a log scale. NOEL is plotted on the x-axis. The higher and further to the left a compound is on the graph means that it has a lower ratio of NOEL to LED, which would be predictive of a compound that would not be likely to have a good safety margin. The lower and further to the right a compound is on the graph means that it has a higher ratio of NOEL to LED, which would be predictive of a compound that would be more likely to have an acceptable safety margin. (Tr. at 792:16-795:6 (Eastman Dir.); PTX 148 at PG78507; P-36b).

375. The only compound out of the hundreds P&G tested with a NOEL to LED ratio, or safety margin, between 1,000:1 and 10,000:1 was risedronate (shown above as "3-Pyr HEDP"), indicating that it had the greatest chance of succeeding as a safe and effective compound for treatment in humans. (Tr. at 795:7-795:18, 796:9-11 (Eastman Dir.); PTX 148 at PG 78507; P-36b).

376. 2-pyr EHDP (shown above as "2-Pyr HEDP") had a NOEL to LED ratio, or safety margin, between 100:1 and 1,000:1. This difference indicates that 2-pyr EHDP would be less likely than risedronate to have an acceptable safety margin. (Tr. at 795:19-796:8 (Eastman Dir.); PTX 148 at PG 78507; P-36b).

377. P&G's testing showed risedronate to have an NOEL to LED ratio, or safety margin, that is ten times better than 2-pyr EHDP and more than 30 times better than 4-pyr EHDP. (Tr. at 867:10-868:20 (Miller Dir.); P-40; PTX 148 at PG 78507; P-36b).

378. The important differences in NOEL to LED ratio, or safety margin, among the three positional isomers of pyr-EHDPs could not have been known or predicted by

any means other than to experimentally test each compound. (Tr. at 869:8-13 (Miller Dir.)).

379. Of all the compounds that P&G tested in the mid-1980s, risedronate was the best drug candidate for advancement toward clinical development by a clear margin. (Tr. at 869:14-870:12 (Miller Dir.); PTX 148 at PG 78507; P-36b).

380. Risedronate's ten-fold better safety window over 2-pyr EHDP indicates great therapeutic advantages for risedronate over 2-pyr EHDP, and this difference in therapeutic advantage could not have been expected or predicted by a person of ordinary skill in the art in the mid-1980s, nor could it likely be predicted even today. (Tr. at 870:4-871:9 (Miller Dir.)).

381. PTX 44 is a biweekly report prepared by Dr. Benedict dated January 24, 1986, entitled "New Diphosphonates and Structure/Activity Relationships." Dr. Benedict prepared PTX 44 in the ordinary course of business, and it was his ordinary course to prepare such reports. (Tr. at 477:16-478:8 (Benedict Dir.); PTX 44).

382. Regarding risedronate, Dr. Benedict wrote:

> Several compounds have come through the screens looking very interesting; one especially to me, 2-(3-pyridyl)-1-hydroxyethane-1,1-bis(phosphonate). 3-pyridyl EHDP seems to exhibit very high potency with what at this point looks like a safety profile similar to 2-pyridyl EDP. This combination, if it holds up, would lead to a drug having a very large therapeutic index.

(Tr. at 478:9-479:3 (Benedict Dir.); PTX 44).

383. The goal of Dr. Benedict's work over the prior several years had been to find a compound that would have a wide therapeutic index-that is, a compound that could be dosed at a low enough level that it would not inhibit bone mineralization. Risedronate was "very interesting" to Dr. Benedict because it "was the best compound that [P&G]

had found" that combined the efficacy (*i.e.*, activity as an inhibitor of bone resorption) that would enable P&G to minimize the problems with bone mineralization, without any undesirable toxic effects. (Tr. at 479:4-19 (Benedict Dir.); PTX 44).

384. Dr. Benedict further observed:

> One just have to believe that these structure/activity observations are telling us something important about the mechanisms of action of these drugs; about how they are binding to some important 'receptor' or enzyme site and effecting an important cellular process in the osteoclasts.

At the time Dr. Benedict wrote this sentence, he had devoted approximately 14 years to finding a new bisphosphonate for treatment of bone disease. (Tr. at 479:20-480:11 (Benedict Dir.); PTX 44).

385. Based upon the test results showing that risedronate was "very potent" and suggesting that it was going to be safe, along with the fact that it was relatively easy to synthesize, Dr. Benedict recommended that P&G select risedronate as its lead compound for further development. (Tr. at 482:11-483:4 (Benedict Dir.)).

VI. THE INVENTION DESCRIBED AND CLAIMED IN THE '122 PATENT

386. The '122 patent aims to solve problems encountered with prior art bisphosphonates, including EHDP, APD, and Cl_2MDP. In particular, the '122 patent observes that while "[bis]phosphonates tend to inhibit the resorption of bone tissue, which is beneficial to patients suffering from excessive bone loss . . . EHDP, APD and many other prior art [bis]phosphonates have the propensity of inhibiting bone mineralization when administered at high dosage levels." (JTX 1, col. 2:2-7).

387. The object of the invention of the '122 patent is

> to develop more biologically potent [bis]phosphonate compounds that can be administered a low dosage levels which cause little or no mineralization inhibition, thereby

> resulting in a wider margin of safety. Low dosage levels are also desirable to avoid the gastro-intestinal discomfort (like diarrhea) sometimes associated with oral administration of large quantities of [bis]phosphonates.

(JTX 1, col. 2:11-18).

388. The '122 patent teaches the design and synthesis of a novel class of bisphosphonate compounds and their use in treating osteoporosis. (Tr. at 610:1-3 (McKenna Dir.); JTX 1).

389. The compounds described in the '122 patent are geminal bisphosphonic acid compounds, or their pharmaceutically-acceptable salts and esters, in which the biphosphonic acid-containing carbon is linked to a six-membered aromatic ring containing one or more nitrogen atoms, with pyridine rings being the most preferred. (JTX 1, col. 3:44-52).

390. According to the '122 patent, the compounds of the present invention

> may provide one or more of the following advantages over the art-disclosed [bis]phosphonates of (1) being more potent in inhibiting bone resorption; (2) possessing less potential for inhibition of bone mineralization, since mineralization inhibition is believed to be predominantly a mass related physico-chemical effect; (3) having generally a wider margin of safety (i.e., wider dosing interval between the lowest effective antiresorptive dose and the lowest dose producing mineralization inhibition); (4) allowing lower oral dosages to be administered, thereby avoiding the gastro-intestinal discomfort (like diarrhea) sometimes associated with higher dosages of [bis]phosphonates; and (5) having potential for flexibility of dosing methods.

(JTX 1, col. 11:7-20).

391. Risedronate is one of the compounds claimed by the '122 patent. (*See, e.g.*, JTX 1, col. 18:22-24 (claim 4).

VII. THE INVENTION AND TEACHINGS OF THE '406 PATENT

A. The Invention of the '406 Patent

392. U.S. Patent No. 4,761,406 (the "'406 patent") discloses an "on-off" dosing regimen for administering bisphosphonates to a patient. The dosing regimen includes a first period of administering the bisphosphonate of from 1 to 90 days, followed by a rest period of about 50 to 120 days where no bisphosphonate is administered to the patient. (JTX 5, col. 2:67-col. 3:8; Tr. at 608:12-18 (McKenna Dir.); Tr. at 871:24-872:10 (Miller Dir.)).

393. The '406 patent discloses a generic formula for a family of geminal bisphosphonates that have substitutions on the geminal carbon atom. (JTX 5, col. 4:40-50; Tr. at 462:14-463:4 (Benedict Dir.)).

394. Dr. Benedict is not named as an inventor on the '406 patent. He first saw the '406 patent about a year before trial in Delaware in November 2006. (Tr. at 462:3-5; 462:10-13 (Benedict Dir.)).

B. The Teachings of the '406 Patent

395. The '406 patent teaches:

> The ability of polyphosphonates to inhibit bone loss has been well documented in animals and man. However, these compounds have, thus far, not proven to be particularly useful in diseases such as osteoporosis where there is chronic loss of bone, and therefore a perceived need for chronic treatment. The reason for this probably lies in the tight coupling between the bone resorption and formation in the human skeleton. When one attempts to chronically manipulate one phase of the skeletal remodeling cycle (bone resorption or formation), a similar effect occurs in the opposing process and any change produced [is] then negated. In the case of polyphosphonates, chronic inhibition of bone resorption tends to produce chronic inhibition of bone formation. Furthermore, long-term chronic inhibition of remodeling is

> not desirable since it appears that this may lead to the development of spontaneous bone fractures.
>
> It has now been discovered that bone loss can be inhibited and bone mass can be increased if certain polyphosphonates are given, in a limited amount, according to a specific regimen of intermittent, rather than chronic, dosing.

(JTX 5, col. 1:59-2:12).

396. The '406 patent addresses the problem with the then-existing bisphosphonates that, although they might have useful bone antiresorption activity, they had the undesirable side effect of also inhibiting bone mineralization. (Tr. at 609:2-9 (McKenna Dir.)).

397. The '406 patent teaches that, by using a cyclic regimen of administering bisphosphonates, it is possible to achieve a separation of the benign effect of antiresorption from the unwanted side effect of antimineralizaiton. (Tr. at 609:10-17 (McKenna Dir.)).

398. The '406 patent would have led one skilled in the art to believe that, in order to achieve a separation of the effect of the bisphosphonate on bone resorption and mineralization, it was necessary to apply the intermittent dosing regimen described in the '406 patent. (Tr. at 611:1-5 (McKenna Dir.)).

399. The '406 patent contains a list of thirty-six compounds with which the intermittent dosing regimen taught by the '406 patent may be used. (JTX 5, col. 4:65-col. 5:39). Column 5, lines 40-55 contains a list of the eight preferred compounds. (JTX 5, col. 5:40-55). No one compound is specified or particularly called out. (Tr. at 611:19-22 (McKenna Dir.)).

400. Claims 17, 18, and 19 of the '406 patent each claim a method of treatment specially using only one of the eight preferred compounds, including EHDP, hexane-6-amino-1-hydroxy-1,1 diphosphonic acid ("AHDP"), and dichloromethane diphosphonic acid ("Cl_2MDP"). (JTX 5, col. 19:7-col. 20:2; Tr. at 706:23-708:7). There is no specific claim in the '406 patent claiming use of only 2-pyr EHDP. (JTX 5, col. 17:32-col. 19:15; Tr. at 708:1-7 (McKenna Redir.)).

401. The '406 patent does not disclose risedronate (3-pyr EHDP). However, it does disclose 2-pyr EHDP, which it defines as "pyr-EHDP". (JTX 5, col. 5:23; Tr. at 463:5-11 (Benedict Dir.)).

402. The '406 patent does not provide any information on the structure-activity relationships of bisphosphonates. (Tr. at 611:6-9 (McKenna Dir.)).

403. The '406 patent does not accord any significance to the presence of a nitrogen atom in any compound. (Tr. at 611:23-612:1 (McKenna Dir.)). Several of the preferred compounds - including EHDP, Cl_2MDP and HIP-do not contain a nitrogen atom. (Tr. at 612:4-7 (McKenna Dir.); JTX 5, col. 5:42-43, 54).

404. The '406 patent does not suggest anything about the significance of the length of the linking chain between the nitrogen and geminal carbon atom in a bisphosphonate. (Tr. at 612:6-19 (McKenna Dir.)). The list of preferred compounds does not evidence any preferred distance or any pattern as to such distance. (Tr. at 612:20-613:11 (McKenna Dir.)). Instead, the nitrogen-containing compounds listed as preferred have varying chain lengths-in APD, the linker chain has 2 carbon atoms, (JTX 5, col. 5:44-45); in AHDP, it is 5 carbon atoms, (JTX 5, col. 5:46-47); in ABDP, it

is 3 carbon atoms, (JTX 5, col. 5:48-49); and, in pyr-EDP and pyr-EHDP, it is 1 carbon atom, (JTX 5, col. 5:50-53). (Tr. at 613:1-11 (McKenna Dir.)).

405. The '406 patent does not provide any indication that bisphosphonates containing a pyridyl ring are particularly advantageous. While two of the preferred compounds have a pyridyl ring (pyr-EDP and pyr-EHDP), three of the nitrogen-containing compounds (APD, AHDP and ABDP) do not have such a ring. (Tr. at 613:15-19 (McKenna Dir.); JTX 5, col. 5:40-55).

406. There is also variability among the substituents on these Preferred compounds. For example, the first listed compound (EHDP) contains a methyl group; the second (Cl_2MDP) contains a chlorine; the next three compounds (APD, AHDP, and ABDP) have amino groups attached by hydrocarbon linkers of various lengths; the next two compounds (pry-EDP and pyr-EHDP) have pyridine rings; and the last compound (HIP) has a hydrocarbon ring incorporated in the bisphosphonate structure. (Tr. at 614:24-615:12 (McKenna Dir.); JTX 5, col. 5:40-55).

407. There is nothing in the '406 patent that would have led a person skilled in the art to select the 2-pyr EHDP compound over the others identified to use for treatment of bone disease. (Tr. at 614:2-6 (McKenna Dir.)).

408. The '406 patent actually would have taught away from the 2-pyr EHDP compound and other pyridyl compounds because each of these compounds were disclosed to have toxicity problems. (Tr. at 706:11-16 (McKenna Redir.); Tr. at 872:21-874:14 (Miller Dir.); JTX 5 (Col. 13, Table III)).

409. The '406 patent indicates that 2-pyr EHDP is "lethally toxic at 1 mg P/kg/day." It further indicates that two other compound containing pyridyl rings-N-(2-

pyr) AMDP and pyr-EDP (*i.e.*, 2-pyr EDP)-were "lethally toxic at 1 mg P/kg/day." (Tr. at 872:21-874:14 (Miller Dir.); JTX 5 (Col. 13, Table III)).

410. The '406 patent reflects the toxicity results for 2-pyr EHDP that were reported to Dr. Benedict in approximately May 1985 and that were discussed in PTX 507. (Tr. at 463:5-464:7 (Benedict Dir.)).

VIII. DIFFERENCES BETWEEN THE '122 PATENT AND THE '406 PATENT

A. Differences in the Teachings of the '122 Patent and the '406 Patent

411. The '406 patent teaches the use of an intermittent or cyclic regimen for dosing polyphosphonates, and lists compounds that can be used with that regimen. (Tr. at 608:8-609:1, 614:2-23 (McKenna Dir.); Tr. at 87:23-88:4 (Lenz Dir.)).

412. The '122 patent does not claim, teach, suggest or make any reference to the use of an intermittent dosing regimen. (*See* JTX 1; Tr. at 609:21-24 (McKenna Dir.)).

413. The '406 patent suggests that, in order to deal with the problem of separating the beneficial effects of bisphosphonates from their detrimental effects (*i.e.*, the effect on mineralization), one should take existing compounds and alter with the dosage regimen. (Tr. at 633:21-634:12 (McKenna Dir.)).

414. Teva's expert, Dr. Lenz, agreed that "[t]he heart of the invention [of the '406 patent] is administering polyphosphonates" by an intermittent dosing regimen. (Tr. at 254:12-16 (Lenz Cross)).

415. The '406 patent does not teach any new chemical entities. (Tr. at 609:18-20 (McKenna Dir.)).

416. The '122 patent teaches the design and making of new chemical compounds, and in particular, novel bisphosphonates. The '406 patent does not. (Tr. at 609:18-610:3 (McKenna Dir.)).

B. Differences between '406 and '122 Patent claims

417. Claims 4, 16 and 23 of the '122 patent recite a chemical compound (risedronate), a pharmaceutical composition comprising risedronate at a level providing from 0.001 to 600 milligrams composition and a pharmaceutically acceptable carrier, and a method of treating diseases associated with abnormal calcium and phosphate metabolism comprising administering risedronate in a safe and effective amount. (JTX 1, col. 18:22-24, col. 20:54-56, col. 22:5-8).

418. Claim 15 of the '406 Patent recites:

> 15. A method for treating osteoporosis, in humans or lower animals afflicted with or at risk to osteoporosis, comprising administering to said human or lower animal an effective amount of a bone resorption inhibiting polyphosphonate, wherein the bone resorption inhibiting polyphosphonates, and daily dosage ranges, are selected from the group consisting of:
>
> ethane-1-hydroxy-1,1-diphosphonic acid: from about 0.25 mg P/kg to about 4 mg P/kg;
>
> dichloromethane diphosphonic acid: from about 0.12 mg P/kg to about 5 mg P/kg;
>
> Propane-3-amino-1-hydroxy-1,1-diphosphonic acid: from about 0.025 mg P/kg to about 1 mg P/kg;
>
> Butane-4-amino-1-hydroxy-1,1-diphosphonic acid: from about 0.0025 mg P/kg to about 0.1 mg P/kg;
>
> Hexane-6-amino-1-hydroxy-1,1-diphosphonic acid: from about 0.025 mg P/kg to about 1 mg P/kg;
>
> 2-(2-pyridyl-ethane-1,1-diphosphonic acid: from about 0.0025 mg P/kg to about 0.1 mg P/kg;
>
> 2-(2-pyridyl)-1-hydroxy-ethane-1,1-diphosphonic acid: from about 0.00025 mg P/kg to about 0.01 mg P/kg; and/or
>
> Hexahydroindan-2,2-diphosphonic acid: from about 0.25 mg P/kg to about 10 mg P/kg;
>
> and their pharmaceutically-acceptable salts and esters, according to the following schedule:

> (a) a period of from about 1 day to about 90 days during which said bone resorption inhibiting polyphosphonate is administered daily in a limited amount; followed by
>
> (b) a rest period of from about 50 days to about 120 days; and
>
> (c) repeating (a) and (b) two or more times where a net increase in bone mass said human or animal results.

419. Claim 15 of the '406 patent differs from claims 4, 16, and 23 of the '122 patent in that claim 15 of the '406 patent describes a method for treating osteoporosis that involves administering one of eight possible different compounds, none of which is risedronate, according to particular dosage ranges and a particular dosing schedule, while claims 4, 16, and 23 are focused on one particular drug. (Tr. at 629:16-633:13 (McKenna Dir.)).

420. The dosage range of the active ingredient in claim 15 of the '406 patent for 2-pyr EHDP is narrower than the dosage range of active ingredient for risedronate in claim 16 of the '122 patent. (Tr. at 631:5-14 (McKenna Dir.)).

421. Dr. Lenz agreed that the dose range claimed in claim 23 of the '122 patent is "quite enormous" and that the dose range of claim 15 of the '406 patent is narrower than the dose range claimed in claim 23 of the '122 patent. (Tr. at 261:6-20 (Lenz Cross)).

422. Dr. Lenz admitted that there is no suggestion in the '406 patent of a dose range as large as the range claimed in claim 23 of the '122 patent. (Tr. at 261:21-24 (Lenz Cross)).

IX. DIFFERENCES BETWEEN RISEDRONATE AND PRIOR ART BISPHOSPHONATES

A. Small Changes Can Have Unpredictable Effects

1. Examples of Small Changes which have Significant Effects

423. Small changes in chemical structure can have profound effects on the properties of a compound. (Tr. at 597:14-19 (McKenna Dir.); Tr. at 203:16-21 (Lenz Cross)).

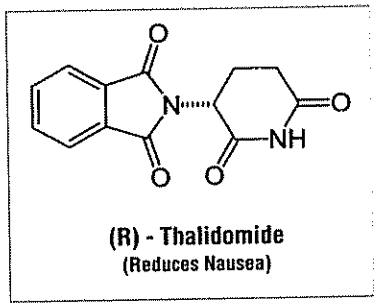
424. Dr. Lenz agreed that even changing just one element can affect the physical, chemical and pharmacological properties of a compound. (Tr. at 204:5-14 (Lenz Cross)).

425. For example, water is a compound safe for human consumption. If a single oxygen atom is changed to a sulfur atom, hydrogen sulfide is produced, which is malodorous and highly toxic. (Tr. at 597:24-598:4 (McKenna Dir.)).

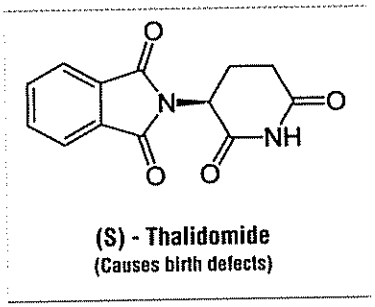
426. If one hydrogen atom in a water molecule is replaced by a methylene group (-CH2-), methanol is obtained. Methanol is known as "wood alcohol" and is extremely toxic. (Tr. at 598:9-13 (McKenna Dir.)). However, if a second methylene group is added, methanol becomes ethanol. (Tr. at 598:17-599:2 (McKenna Dir.)). This compound is safe for human consumption and is present in alcoholic beverages. (Tr. at 599:2-3 (McKenna Dir.)). From ethanol, if another methylene group is added, the compound becomes propanol, which again is toxic. (Tr. at 599:10-12 (McKenna Dir.)). Alternatively, if a hydroxy (–OH) group is substituted for one hydrogen (-H) in ethanol, the compound is ethylene glycol, which is antifreeze and is extremely toxic. (Tr. at 598:9-600:3 (McKenna Dir.)).

427. Dramatic changes in properties may also be obtained without changing any of the atoms in the compound. One example of this is stereoisomers, which have the same composition and same number of atoms. Enantiomers are a type of stereoisomer in which the two compounds are indistinguishable with respect to their physical and chemical properties, except that they are structurally mirror-images of one another, analogous to a person's right and left hand. They look the same but cannot be put on top of each other. Enantiomers are indistinguishable with respect to their physical and chemical properties. However, even though enantiomers have the same identical formula, and the same molecular weight, pairs of such stereoisomers may have significantly different biological reactions. (Tr. at 600:10-602:10 (McKenna Dir.)).

428. One example of this is thalidomide. The structures of the two enantiomers of thalidomide are:



(R) - Thalidomide
(Reduces Nausea)



(S) - Thalidomide
(Causes birth defects)

Although the two compounds look like the same compound, it has been shown that one of the stereoisomers is responsible for one biological effect, namely alleviating nausea in pregnant women, while the other caused tragic birth defects. (Tr. at 601:24-602:19 (McKenna Dir.); P-32).

429. In terms of structural similarity, enantiomeric pairs are much closer structurally than risedronate is to 2-pyr EHDP. (Tr. at 603:17-604:1 (McKenna Dir.)).

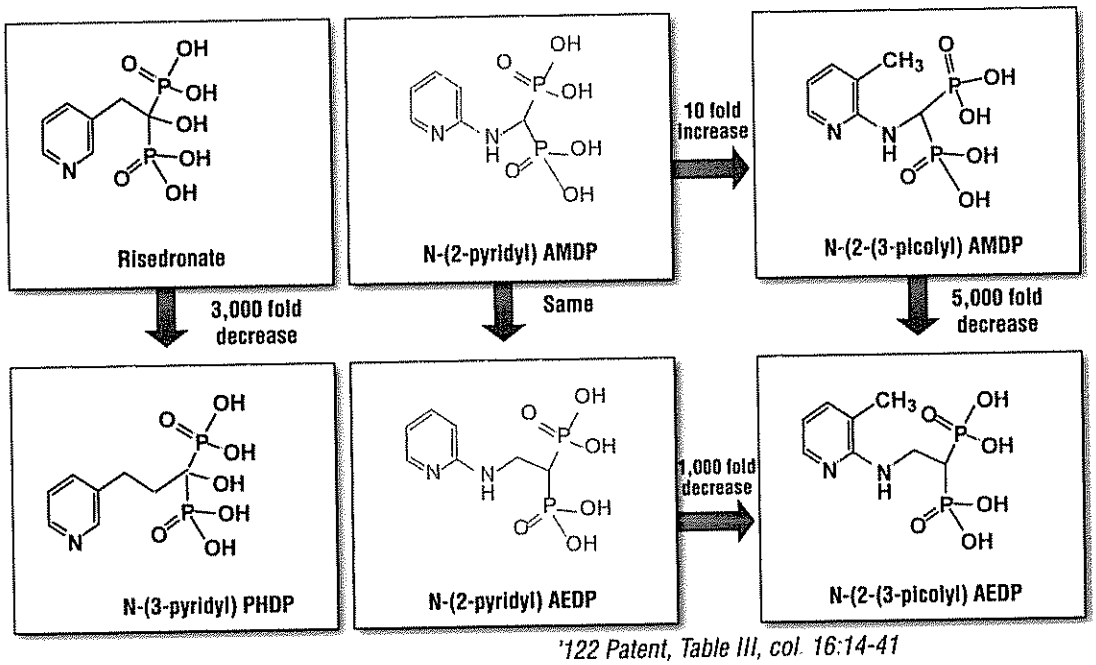
2. Dr. Lenz Has Obtained Patents Based on the Recognition that Small Changes Can Be Significant.

430. Dr. Lenz is the sole named inventor of U.S. Patent Nos. 4,013,644 (the "'644 patent") and 4,013,666 (the "'666 patent"). The '644 patent was filed on March 15, 1976 and the '666 patent was filed one day later, on March 16, 1976. Both of these patents issued on the same day in March 1977. Claim 1 of both the '644 and '666 patent claims a generic formula for a pharmaceutical compound in which Z can be phenyl and R can be hydrogen. Where Z is phenyl and R is hydrogen, the compounds claimed by these patents differ only in that the '644 patent claims a compound with an additional double bond. (Tr. at 225:4-226:12 (Lenz Cross); PTX 464; PTX 465).

431. Despite the structural similarity between the compounds claimed in the '644 and '666 patents, Dr. Lenz characterized these compounds as new, useful and nonobvious inventions. (Tr. at 227:10-227:14 (Lenz Cross)).

3. Small Changes in the Structure of Bisphosphonates Can Have Dramatic Effects on Their Activities

432. There are also many examples of structurally similar bisphosphonates that have different activities. For example:



'122 Patent, Table III, col. 16:14-41

This illustration shows the effect on efficacy of small changes in the structure of bisphosphonates. As shown in the first pair, adding one methylene unit to risedronate to form N-3-pyridyl PHDP reduced activity 3,000 times. By contrast, as shown by the middle pair of compounds, starting with N-2-pyridyl AMDP and adding one methylene unit to the linking chain to form N-2-pyridyl AEDP had no effect on the efficacy of the bisphosphonate compound. On the other hand, starting with N-2-pyridyl AMDP and adding a methyl unit at the "3" position of the pyridine ring to form N-2,3-picolyl AMDP produced a compound with 5 times more activity. However, starting with N-2-pyridyl AEDP and making the same substitution (*i.e.*, adding a methyl unit at the "3" position of the pyridine ring) to form N-2,3-picolyl AEDP produced a compound with 1,000 times less activity. Finally, taking the N-2,3-picolyl AMDP and lengthening the chain with the addition of one methylene unit resulted in a 5,000 fold decrease in activity. (Tr. at 604:2-607:19 (McKenna Dir.); P-31).

433. These examples are consistent with the statements of Dr. Fleisch that it is difficult to discern any reliable structure-activity relationships with bisphosphonates. (Tr. at 607:20-608:2 (McKenna Dir.)).

B. Differences between Risedronate and 2-pyr EHDP

434. While 2-pyr EHDP and risedronate(*i.e.*, 3-pyr EHDP) may appear similar in a 2-dimensional depiction, such a representation does not accurately represent the size, shape, and properties of a molecule. (Tr. at 593:4-15 (McKenna Dir.)).

435. As a result of the difference in location of the nitrogen, 2-pyr EHDP and 3-pyr EHDP would have different physical, chemical, and biological properties. (Tr. at 594:8-11 (McKenna Dir.)). For example, there would be differences in charge distribution, polarity and hydrogen bonding. (Tr. at 594:5-7, 594:12-595:13 (McKenna Dir.)). These differences "could have very profound effects at different levels of pharmacological action." (Tr. at 593:20-595:20 (McKenna Dir.)).

436. Dr. Lenz conducted no tests to determine whether the properties of risedronate and 2-pyr EHDP are either similar or different. (Tr. at 205:11-18 (Lenz Cross)). Specifically, Dr. Lenz did not conduct a single test or model to compare the charge distribution, polarity properties, chelation properties, or basicity of the two compounds. (Tr. at 262:9-19, 264:12-17 (Lenz Cross).

437. In the mid-1980s, based on the structures of 2-pyr EHDP and risedronate, one skilled in the art would not have expected these two compounds to have similar efficacy. Nor would one of ordinary skill in the art at that time have been able to predict the relative efficacies of the two compounds given the lack of understanding of the mechanism of action. (Tr. at 595:21-596:8 (McKenna Dir.)).

438. In the mid-1980s, one of ordinary skill in the art would not have expected that modifying 2-pyr EHDP to form risedronate would have produced a compound with improved biological properties. At that time, no reliable structural activity relationship for bisphosphonates had been developed. Moreover, those skilled in the art recognized that the activity of these bisphosphonates was highly unpredictable. (Tr. at 615:13-616:9 (McKenna Dir.)).

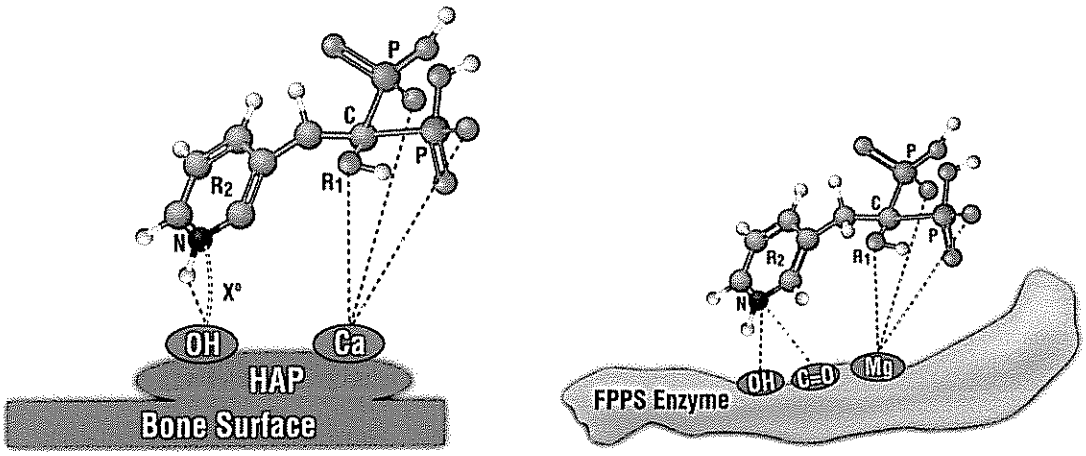
439. In the mid-1980s, based on the structures of 2-pyr EHDP and risedronate, one skilled in the art would not have expected the two compounds to have the same toxicity. Nor would one of ordinary skill in the art have been able to predict the relative toxicities of the two compounds. (Tr. at 596:16-597:1, 616:10-17 (McKenna Dir.)).

C. New Information about The Mechanisms of Action of Bisphosphonates Demonstrates the Significance of the Difference in Structure Between 2-pyr EHDP and Risedronate

440. Over the past five years, researchers have gained a greater understanding of the mechanisms of action of bisphosphonates, and as a result a better understanding the effect of changes in structure have on a compound's activity. (Tr. at 566:12-15 (McKenna Dir.)).

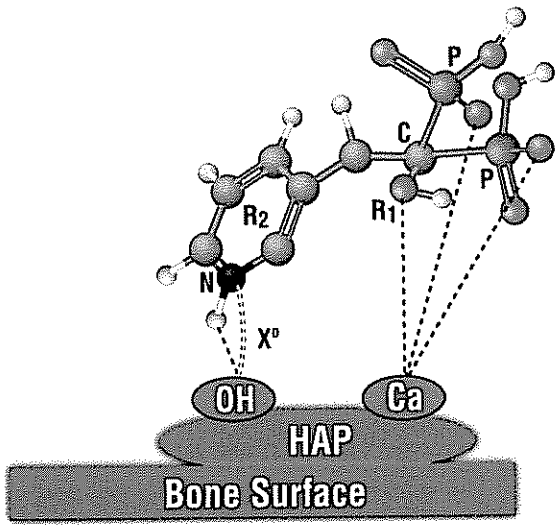
441. For nitrogen-containing bisphosphonates, such as risedronate, there are two potential sites of interaction which in combination determine the drug's activity. (Tr. at 581:14-21 (McKenna Dir.)).

442. These two mechanisms are illustrated below:



The first mechanism of action involves interaction of the bisphosphonate with hydroxyapatite (or "HAP"), which is a mineral that constitutes the bone surface. (Tr. at 581:23-582:12 (McKenna Dir.); Slide P-22). The second mechanism involves interaction of the bisphosphonate with an enzyme called farnesyl phyrophysiophate synthesis ("FPPS"), which plays a role in the bone remodeling process. (Tr. at 582:13-24, 587:17-588:8 (McKenna Dir.); Slide P-22).

443. The following figure illustrates the interaction of a bisphosphonate (in this case risedronate) with HAP:



As shown in the above illustration, calcium ions on the bone surface interact with one oxygen on each of the two phosphonate (PO_3) groups of the bisphosphonate, as well as with the oxygen of the hydroxyl (OH) group. (Tr. at 581:23-582:2, 584:1-9 (McKenna Dir.); Slide P-24).

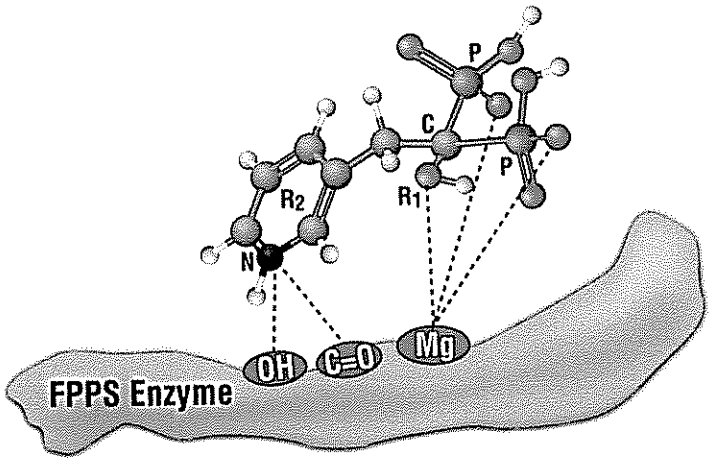
444. In addition, it recently was discovered that there is an interaction between the nitrogen in the pyridine ring of a pryridyl bisphosphonate and an oxygen on the HAP at the surface of the bone. (Tr. at 584:12-17 (McKenna Dir.); Slide P-24). In this interaction, the angle that is formed by the nitrogen atom through the hydrogen to the oxygen at the bone surface is critical. (Tr. at 585:2-6 (McKenna Dir.); Slide P-24). If the angle is too small, the bond between the nitrogen and oxygen atoms is weak or non-existent. (Tr. at 585:7-8 (McKenna Dir.)). The position of the nitrogen in the bisphosphonate will affect the size of this angle. (Tr. at 584:18-585:1 (McKenna Dir.)). For example, comparing risedronate to a compound in which the nitrogen is on the 2-position in the pyridyl ring, nitrogen in the 2-position actually has better affinity to bone. (Tr. at 585:7-15 (McKenna Dir.)).

445. A bisphosphonate needs to bind to bone in order to be effective; however, if it binds too strongly, it may reside in the bone longer, which could have adverse consequences for a drug that is being taken long term. (Tr. at 585:16-586:4 (McKenna Dir.)).

446. The second mechanism by which nitrogen-containing bisphosphonates work is by inhibiting activity of an enzyme called FPPS. (Tr. at 582:13-20 (McKenna Dir.)). Inhibiting FPPS blocks a biochemical pathway, called the mevalonic pathway, which mediates the actions of the osteoclasts, the cells responsible for bone erosion. (Tr. at 587:20-588:8 (McKenna Dir.)). In doing so, FPPS causes the osteoclast to die, thereby mitigating the bone erosion (*i.e.*, bone resorption) process. (Tr. at 587:20-588:8 (McKenna Dir.)).

447. The existence of this second mechanism of action just unfolded over the last several years. (Tr. at 589:2-6 (McKenna Dir.)).

448. The following figure illustrates the interaction of a bisphosphonate (here, risedronate) with the FPPS enzyme:



The oxygen atoms in each of the phosphonate groups of a bisphosphonate, along with the oxygen atom in the hydroxy group, bind to a magnesium ion present in the FPPS enzyme. In addition, for nitrogen-containing bisphosphonates, a bond is formed between the nitrogen of the bisphosphonate and two oxygen atoms that are present in the enzyme. In this interaction, the length of the bond between the nitrogen and the oxygen atoms is critical; if the bond length is too long, the interaction will be lost. (Tr. at 587:10-589:1 (McKenna Dir.); Slide P-23).

449. This interaction of bisphosphonates with the FPPS enzyme explains the differences in potency between various types of bisphosphonates. (Tr. at 587:11-16 (McKenna Dir.)).

450. Enzyme inhibition can be analogized to a "lock and key". The enzyme is like the lock, and the drug is like the key. The key will only fit into the lock and turn the tumblers if it has exactly the right shape. Certain compounds will be better "keys" and thus better fits into the enzyme active site, or "lock." If the "key," or compound, does not fit as well, then there will not be the necessary interactions at the active sites on the

enzyme. In other words, it may fail to bind or may not bind as well. (Tr. at 589:16-591:15 (McKenna Dir.)).

451. In the case of nitrogen-containing bisphosphonates, the location of the nitrogen is "critical" in order to achieve the right bond length and thus the right interaction between the nitrogen and the oxygens at the active site. (Tr. at 588:20-589:1 (McKenna Dir.)). Moving the nitrogen even by one position could eliminate or greatly weaken the bond. (Tr. at 591:16-592:6 (McKenna Dir.)).

452. This information was not available in the mid-1980s. This research has only been done over the last several years. (Tr. at 589:5-6 (McKenna Dir.)).

453. Now, in 2006, this research and the importance of the location of the nitrogen in a bisphosphonate helps explain what Dr. Benedict observed about the large differences in potency among the 2, 3 and 4-pyr EHDP compounds. (Tr. at 589:12-15 (McKenna Dir.)). Moving the nitrogen even small distances can make possible or abolish these interactions between the nitrogen of the compound and the oxygen atoms on the surface of the enzyme. (Tr. at 589:13-15 (McKenna Dir.)).

454. Risedronate optimizes the interactions between the nitrogen and the oxygen atoms. Knowing the mechanism of action of the nitrogen-containing bisphosphonates and being able to visualize these interactions using x-ray crystallographic studies of inhibitor-enzyme complexes, the potency of risedronate can now be explained. (Tr. at 591:21-24 (McKenna Dir.)).

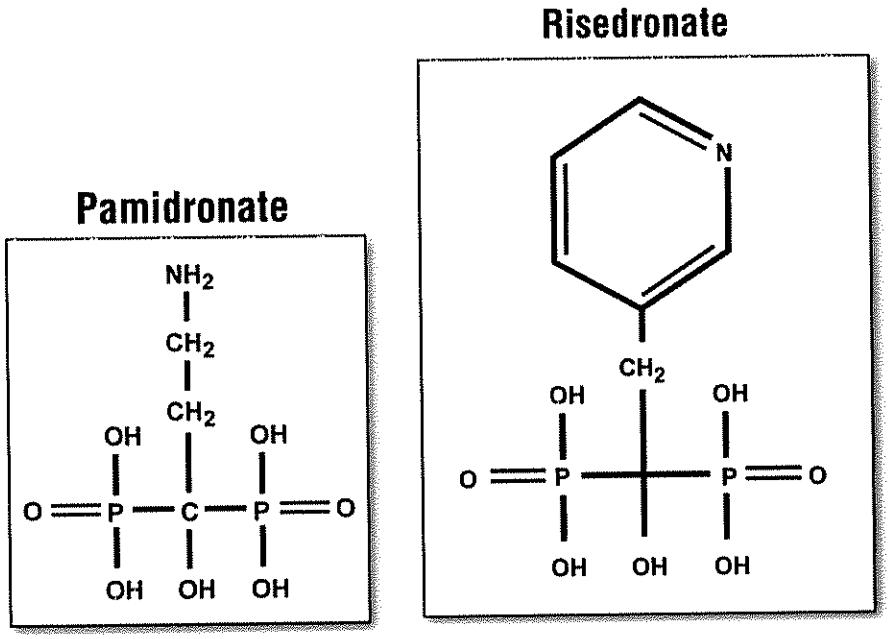
455. If the nitrogen in the pyridyl ring of risedronate is moved to the "2" or "4" position, the interaction between the nitrogen and oxygen atoms will be lost or greatly

weakened. (Tr. at 592:1-4 (McKenna Dir.)). This will affect the ability of the compound to bind to the active site. (Tr. at 592:5-6 (McKenna Dir.)).

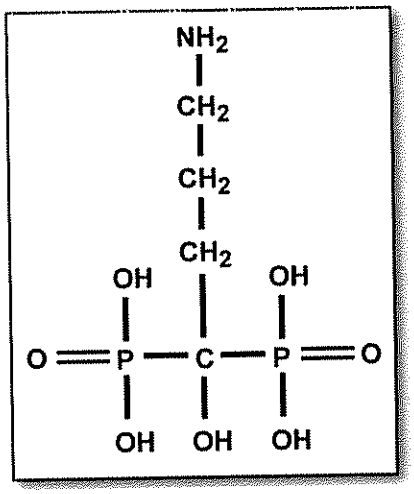
456. However, the information being developed today about the mechanism of action of bisphosphonates does not address pharmacology or toxicology. Even today, there is no useful model for what makes a particular bisphosponate toxic. (Tr. at 597:2-13 (McKenna Dir.)).

D. Differences between Risedronate and Straight Chain Nitrogen-Containing Bisphosphonates

457. Below are two-dimensional representations of pamidronate (top left), alendronate (bottom left), and risedronate (right):



Alendronate



(Tr. at 616:22-617:9 (McKenna Dir.); Slide P-33).

458. While pamidronate, alendronate, and risedronate are all bisphosphonates and all have a hydroxy substituent on the geminal carbon atom, they have important differences. (Tr. at 617:10-18 (McKenna Dir.)).

459. The chemistry of straight chain compounds, like pamidronate and alendronate, is very different from that of pyridine rings, like risedronate. For example, pamidronate and alendronate each have terminal primary amino groups (*i.e.*, a nitrogen atom at the end of a chain of carbon atoms attached to the geminal carbon atom) and thus will be strong bases, while the nitrogen in the pyridine ring of a risedronate is a weak base. As a result, at physiological pH, pamidronate and alendronate would likely be protonated (*i.e.*, include a hydrogen atom) and have a positive charge. Risedronate would not be expected to be protonated or have a positive change. (Tr. at 618:2-16 (McKenna Dir.)).

460. Another difference between pamidronate and alendronate, on the one hand, and risedronate, on the other, is the spatial organization of electrons with respect to

the nitrogen atom. In the case of pamidronate and alendronate, they are organized in a manner that is called "sp3 hybridized," while in the case of risedronate, they are "sp2 hybridized." (Tr. at 618:17-619:3 (McKenna Dir.)).

461. A further difference between straight chain versus pyridine compounds is the carbon-carbon bond angles. (Tr. at 622:12-21 (McKenna Dir.)). The carbon-carbon bond angles in pamidronate and alendronate are 109 degrees because of their hybridization. In risedronate, the carbon-carbon bond angle is 120 degrees. (Tr. at 622:12-21 (McKenna Dir.)).

462. Yet another difference between pamidronate, alendronate and risedronate is the distance between substituents. Bond lengths in a ring are different from those in a straight hydrocarbon chain. (Tr. at 622:22-23 (McKenna Dir.)).

463. Moreover, the straight chain compounds are more flexible, as the straight chain can vary in conformation, while the nitrogen in a pyridine ring is fixed. (Tr. at 620:1-5 (McKenna Dir.)).

464. The structural and chemical differences between pamidronate and alendronate, on the one hand, and risedronate, on the other, can have numerous effects on the biological properties of the compounds. For example, the more basic pamidronate and alendronate could have different gastrointestinal irritation characteristics as compared to risedronate, which is a weak base. In addition, the protonated pamidronate and alendronate are less likely to be transported through cellular membranes than the unprotonated risedronate. Because of these structural and charge differences, they are likely to interact differently with the active site target. For example, they are likely to form different types of hydrogen bonds. (Tr. at 619:4-620:5 (McKenna Dir.)).

465. As a result of these various differences, it is not appropriate to attempt to predict the efficacy of a compound based on "counting carbons." Because of, among other things, the differences in bond lengths, bond angles, and hybridization, the carbons in the straight hydrocarbon chains of pamidronate and alendronate are different chemically from the carbons in the pyridine ring structure of risedronate. Therefore, such carbon counting would be "an incorrect analysis." (Tr. at 621:12-623:2 (McKenna Dir.)).

466. As a result of these differences between straight chain compounds and pyridine ring compounds, one of ordinary skill in the art in the mid-1980s with knowledge of pamidronate and alendronate would not have reasonably expected that modifying 2-pyr EHDP to form risedronate would produce a compound that was safe and effective for treatment of bone disease. At that time, there was no clear-cut structure-activity relationship to guide researchers, there was no understanding of any aspect of the mechanism of action of bisphosphonates, and there was no understanding of how the pharmacology and toxicology of the compounds might differ. (Tr. at 620:6-621:11 (McKenna Dir.)).

E. Differences between Risedronate and Other Pyridyl Art Cited by Teva

467. The chart below provides a summary of eight references cited by Teva that disclose pyridyl compounds for various therapeutic uses.

Reference	Therapeutic Use	Use for Treatment of Osteoporosis	Organophosphorus Compound	Efficacy and Toxicity Data	Data Provided for Series of 2-, 3- and 4-pyridyl versions of a compound
4,004,012 (DTX 45)	Cardiotonic agent	No	No	Efficacy No Toxicity	4-pyridyl only
4,072,746 (DTX 43)	Cardiotonic agent	No	No	Efficacy No Toxicity	4-pyridyl only
3,163,654 (DTX 49)	Analgesic	No	No	No Efficacy No Toxicity	No data
Arch. Pharmazie (DTX 52)	Analgesic	No	No	Efficacy Toxicity	2-pyridyl preferred over 3- and 4-pyridyl for efficacy, fentanyl preferred over any pyridyl for efficacy 4-pyridyl preferred over 2- and 3-pyridyl for toxicity
4,057,636 (DTX 44)	Blood Pressure	No	No	Efficacy Toxicity	3-pyridyl only
3,928,369 (DTX 46)	Depression	No	No	Efficacy Toxicity	Efficacy for 2- and 3- and 4-pyridyl Toxicity for 2- and 3-pyridyl only
3,591,584 (DTX 47)	Inflammation	No	No	No Efficacy No Toxicity	No data
3,225,054 (DTX 48)	CNS stimulants Diuretic Inflammation Cardiac	No	No	No Efficacy No Toxicity	No data

This chart accurately summarizes Dr. McKenna's findings concerning the listed references. The first column identifies the references. The second column lists the principal therapeutic uses indicated in each reference. The third column indicates whether or not the reference disclosed any compounds for use in treating osteoporosis. The fourth column indicates whether or not the reference contained bisphosphonates or other organophosphorus compounds. The fifth column indicates whether or not the reference contained efficacy or toxicity data. The last column addresses whether or not the reference provided data for each of the 2-pyr, 3-pyr, and 4-pyr versions of a compound. (Tr. at 623:9-627:11 (McKenna Dir.); Slide P-34).

468. The therapeutic uses and indications identified in the various references are very diverse, ranging from cardiotonic agents to analgesics to hypertensive agents to depression treatments to treating inflammation to CNS stimulants. (Tr. at 624:5-17 (McKenna Dir.)).

469. As Dr. Lenz admitted, none of the references disclose use of a compound for the treatment of osteoporosis. (Tr. at 624:18-23 (McKenna Dir.); Tr. at 267:3-8, 268:2-9,269:1-9; 270:8-13, 271:16-21, 272:16-23, 274:6-14 (Lenz Cross)).

470. In trying to determine structure-activity relationships of various compounds, it would not be reasonable to make comparisons between drugs intended for completely different indications, even though they may contain certain structural similarities. (Tr. at 624:12-17 (McKenna Dir.)).

471. As Dr. Lenz also admitted, none of the references disclosed any bisphosphonates or even any organophosphorus compounds. (Tr. at 625:3-5 (McKenna Dir.); Tr. at 267:3-8; 268:2-9, 269:9, 270:8-13, 271:16-21, 272:16-23, 274:6-14, (Lenz Cross)).

472. Indeed, as Dr. Lenz further admitted, the compound structures disclosed in several of these references, (*e.g.*, DTX 44, 45, 46, 47, and 49), differ significantly from the bisphosphonates claimed in the '122 patent. (Tr. at 269:18-24, 270:14-18, 271:22-272:3, 273:1-4 (Lenz Cross)).

473. Not all of the references cited by Dr. Lenz contained both efficacy and toxicity data for each of the 2, 3, and 4-positional pyridyl substituents disclosed. Some of the references contained such data, however, in some cases, there was efficacy data, but not toxicity data. In other cases, there was neither efficacy nor toxicity data. Without such data, it is not possible to construct any idea about structure-activity relationships of these compounds. (Tr. at 625:6-22 (McKenna Dir.)).

474. With respect to the compounds that were actually synthesized and tested, there was no consistent preference for one pyridyl group over another. Some of the

references give data for only one positional isomer. For example, U.S. Patent Nos. 4,004,012 (DTX 45) and 4,072,746 (DTX 43) provide efficacy data for only the 4-pyridyl compound. (Tr. at 626:4-9 (McKenna Dir.)). Some of the references, such as U.S. Patent No. 3,163,654 (DTX 49) contained no data, making it impossible to determine whether any pyridyl group was preferred. One of the references, Arch Pharmazie (DTX 52), suggests that although the 2-pyridyl compound was preferred in terms of efficacy over the 3 and 4-pyridyl versions, the parent compound was preferred over all three. However, with respect to toxicity, the 4-pyridyl compound was preferred over both the 2 and the 3-pyridyl compounds. (Tr. at 625:23-627:6 (McKenna Dir.)).

475. Dr. Lenz agreed that, in some of these patents, the 2-pyridyl version of the compound was preferred over the 3-pyridyl version, while in another data was only given for a 4-pyridyl version. (Tr. at 268:10-13, 270:19-271:2 (Lenz Cross)).

476. Accordingly, there is insufficient data in the references cited by Dr. Lenz to make a coherent judgment as to structure-activity relationships. In those cases where there is data, there is no clear-cut indication as to which position would confer the most benefit. (Tr. at 628:1-8 (McKenna Dir.)).

477. None of these references, alone or in combination, would suggest to a person of ordinary skill in the art to modify 2-pyr EHDP to create risedronate with an expectation that the resulting compound would be effective in treating bone disease in humans. (Tr. at 627:12-18 (McKenna Dir.)).

478. None of these references, alone or in combination, would suggest to a person of ordinary skill in the art to modify 2-pyr EHDP to obtain 3-pyr EHDP with an

expectation that the resulting compound would be safe for use in treating osteoporosis. (Tr. at 627:19-23 (McKenna Dir.)).

479. The references cited by Teva and Dr. Lenz are not representative or typical of the state of the art in the mid-1980s. Dr. McKenna conducted a search of the patent literature for compounds that were listed as drugs and that contained 2, 3, and/or 4-pyridyl substituents for ten years going back from about 1985 or 1986. That search generated 15 references, only three of which described all three pyridyl compounds. (Tr. at 628:9-24 (McKenna Dir.)).

X. SUCCESS OF RISEDRONATE

A. Success of Risedronate in Treating Osteoporosis

480. Based on Dr. Bilezikian's experience, risedronate is highly successful in treating osteoporosis. (Tr. at 381:18-23 (Bilezikian Dir.)).

481. Clinical trials have unequivocally shown that risedronate is effective in reducing major fractures, including hip fractures and vertebral fractures. Moreover, risedronate treats osteoporosis safely. (Tr. at 381:24-382:8 (Bilezikian Dir.)).

482. Risedronate is an extremely potent bisphosphonate. (Tr. at 380:8-9 (Bilezikian Dir.)).

483. Risedronate is a thousand times more potent that etidronate. As a result, it is possible to administer risedronate at a much lower dose than etidronate. (Tr. at 380:5-18 (Bilezikian Dir.)).

484. Being able to treat with a lower dosage level is desirable because it means that a patient is less likely to have adverse consequences. (Tr. at 381:7-17 (Bilezikian Dir.)).

485. Slide P-17 illustrates the difference in therapeutic index, or safety margin, for risedronate and etidronate. Risedronate has an effective dose of 5 milligrams, as compared to an effective dose of 400 milligrams for etidronate. Conversely, the lowest dose that will inhibit mineralization for risedronate is at least 5,000 times greater than the lowest mineralization-inhibiting dose for etidronate. As a result, risedronate has a thousand-fold therapeutic index, as opposed to a two to one therapeutic index for etidronate. (Tr. at 380:14-381:6 (Bilezikian Dir.)).

486. There are no clinical head-to-head studies comparing the therapeutic efficacy of alendronate and risedronate. (Tr. at 384:15-385:2 (Bilezikian Dir.)).

487. There are, however, perceived differences between alendronate and risedronate which play an extremely important role in the clinical use of the drugs. Risedronate is perceived to be better tolerated and therefore not have the same likelihood of causing upper gastro-intestinal irritation as does alendronate. (Tr. at 385:3-386:9 (Bilezikian Dir.)).

488. Alendronate is also known to have a more profound effect on bone turnover than risedronate. This is not necessarily a good thing because it can lead to concerns about "too much of a good thing." That is, there is a perceived risk with alendronate of so-called "frozen bone" syndrome. (Tr. 387:16-388:11 (Bilezikian Dir.)).

489. Frozen bone syndrome leads to bones that are brittle and which break easily. (Tr. at 388:12-20 (Bilezikian Dir.)).

490. As a result of the perceived risk of frozen bone syndrome, physicians in this country now will automatically give their patients who are taking alendronate a so-called "drug holiday" after five years of treatment. That is, patients will take a year off

from taking alendronate. On the other hand, physicians do not give patients who are taking risedronate a drug holiday. (Tr. at 388:12-389:4 (Bilezikian Dir.)).

491. Based on Dr. Bilezikian's experience and expertise, it is his opinion that scientists working in the area of metabolic bone disease in the early and mid-1980s would not have been able to predict these perceived differences between alendronate and risedronate. In Dr. Bilezikian's opinion, there was no way persons of ordinary skill in the art could have predicted the clinical effects of either of these drugs without actually administering them to patients. (Tr. at 390:10-22 (Bilezikian Dir.)).

B. Commercial Success of Risedronate

492. Only one out of 5,000 potential drug compounds synthesized during applied drug research ends up being marketed. (Tr. at 324:3-7 (David Cross); PTX 534 at 207 n.19).

493. Only three out of every ten approved drugs have sales revenue that exceeds the average after-tax development cost of a new drug product. (Tr. at 324:8-12 (David Cross); PTX 534 at 207 n.19).

494. As Teva's economic expert admits, "[s]ometimes...with a blockbuster prescription drug that has performance features clearly due to the patent at issue, the sales and profits generated during the first few year's of the product's life will be sufficiently large to leave little doubt about the patent's commercial success...." (Tr. at 322:7-21 (David Cross); PTX 534 at 201).

495. P&G received FDA approval to market and sell Actonel for the treatment of osteoporosis in April 2000. (Joint Statement ¶ 15.)

496. At the time Actonel was launched, there were already two or three significant competitors in the market for osteoporosis treatments, including Merck's

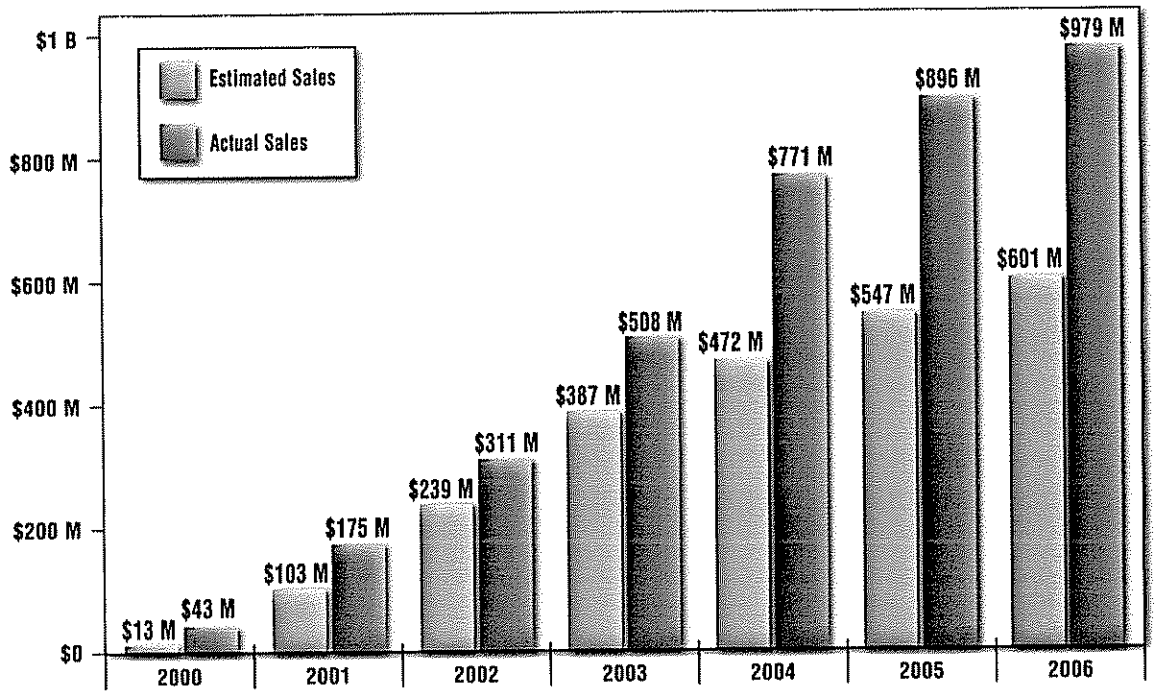
Fosamax and Eli Lilly's Evista. (Tr. at 964:23-965:15, 970:2-8 (Smith Dir.)). Fosamax had been on the market for approximately five years prior to Actonel's entry. (*Id.*)

497. Since that time, Actonel has generated sales of more than $2.7 billion. (Tr. at 962:9-12 (Smith Dir.); DTX 124; P-41).

498. As a result of such sales, Actonel has achieved the status of a "blockbuster drug," *i.e.*, a drug that has sales of a billion dollars or more annually. (Tr. at 962:13-24 (Smith Dir.)).

499. Since its introduction in April 2000, Actonel sales have grown from approximately $43 million in 2000 to almost $900 million in 2005. (Tr. at 963:14-964:22 (Smith Dir.); P-41).

500. Slide P-41 depicts actual and estimated net sales of Actonel from 2000 through 2006:

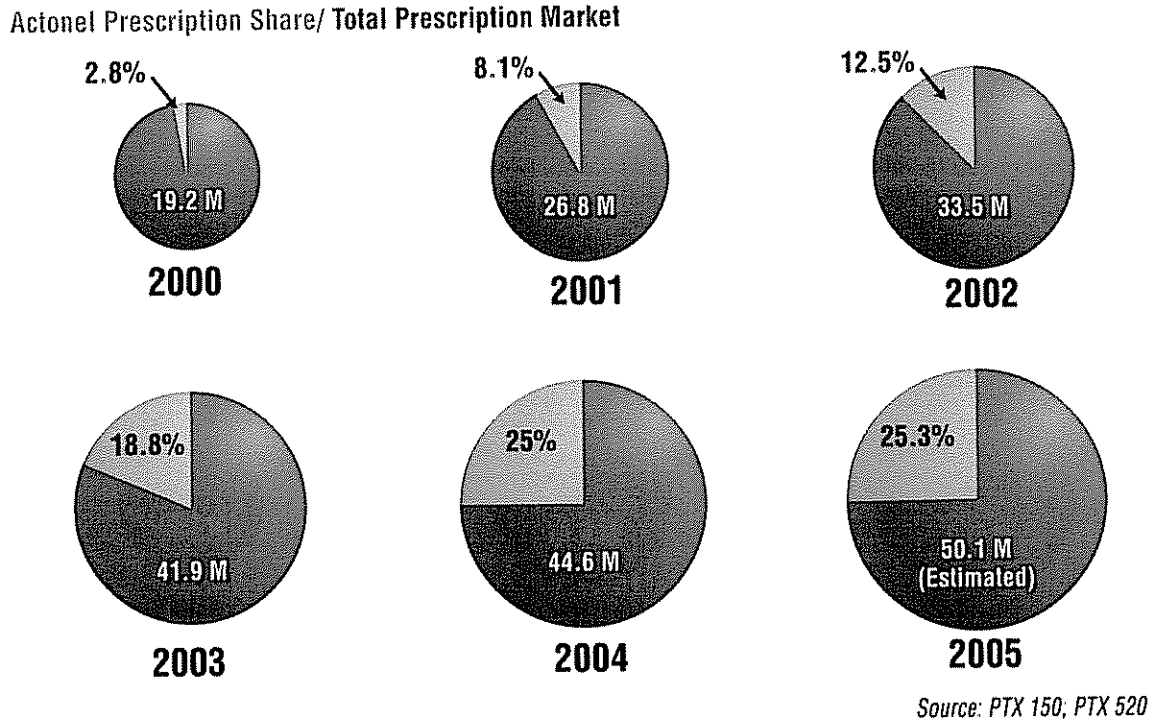


Source: DTX 124; PTX 520

(Tr. at 963-964 (Smith Dir.); DTX 124; PTX 520).

501. During this same period, Actonel's share of the market for osteoporosis treatments grew steadily from 2.8% in 2000, to 8.1% in 2001, to 12.5% in 2002, to 18.8% in 2003, to 25% in 2004, and over 25% in 2005. (Tr. at 967:5-968:11 (Smith Dir.); P-43). Actonel's gain in market share came at the expense of more entrenched competitors, such as Fosamax and Evista. (Tr. at 968:12-969:17 (Smith Dir.)).

502. Slide P-43 depicts Actonel's market share of the total prescription market from 2000 through 2005:



(Tr. at 967-968 (Smith Dir.); PTX 150; PTX 520).

503. In addition, during that time period, Actonel sales consistently outpaced the estimates developed for P&G prior to launch. (Tr. at 965:16-967:4 (Smith Dir.); P-41).

504. The revenues, sales growth, and growth in market share that Actonel has achieved since its launch indicate that Actonel filled an unmet need in the marketplace,

has gained steady acceptance in the marketplace, and is perceived by physicians as offering some benefit over other available osteoporosis treatments. (Tr. at 963:1-13, 964:17-22, 970:2-17 (Smith Dir.)).

505. Evidence of Actonel's total sales, sales growth, growth in market share, and performance compared to estimates uniformly demonstrates that Actonel has been an "unequivocal commercial success." (Tr. at 961:16-962:6, 993:12-20 (Smith Dir.)).

506. In offering his opinion that Actonel is an unequivocal commercial success, Dr. Smith relied on, among other information, PTX 434 (Tr. 955:15-956:1 (Smith Dir.), PTX 322 (*id.* at 956:1-958:10), PTX 523 (*id.* at 973:13-974:9, 988:13-993:11), PTX 230, PTX 231, PTX 232, PTX 233, PTX 243, and PTX 244 (*id.* at 976:16-977:7), DTX 124 (*id.* at 979:7-980:8), and PTX 319, PTX 320, and PTX 321. (*Id.* at 986:7-987:23).

507. Actonel's commercial success was due to the benefits of the invention, as described in the '122 patent. (Tr. at 970:18-971:7 (Smith Dir.)).

508. As an initial matter, P&G communicated the benefits of Actonel in various marketing materials, including sales training materials, brochures, and advertisements. (Tr. at 975:11-978:2 (Smith Dir.); PTX 230; PTX 231; PTX 232; PTX 233; PTX 243; PTX 244). The benefits described in these various materials correspond closely with the benefits claimed in the '122 patent. (*Compare* PTX 244 at PG 95271 ("Actonel helps make bones stronger and less likely to fracture by reducing the effect of the cells that weaken bone") and PTX 231 at PG 95105 ("Actonel decreases bone turnover FAST") & PG 95099 ("Actonel provides proven tolerability") to JTX 1, col. 11, lines 4-20).

509. However, evidence shows that such marketing plays a very limited role in influencing physicians to prescribe a drug. In making prescribing decisions, physicians

are primarily concerned with the well-being of their patients. (Tr. at 954:15-955:14, 957:16-958:10 (Smith Dir.); PTX 322).

510. Physicians are "tough sells" – that is, they are smart, thoughtful, "very sophisticated," skeptical, and base their decisions on "hard evidence," such as clinical data, their own experience prescribing a particular treatment, and experiential data from colleagues, and are not susceptible to persuasive influence. (*Id.*)

511. As a result of these characteristics, pharmaceutical marketing serves largely to disseminate information and to make physicians, and in some cases patients, aware of an available treatment and the attributes of that treatment. (Tr. at 958:11-959:3 (Smith Dir.)). Published studies confirm that detailing and drug sampling has only a minimal long-term impact on the sales of that product. (Tr. at 956:2-958:10 (Smith Dir.); PTX 322).

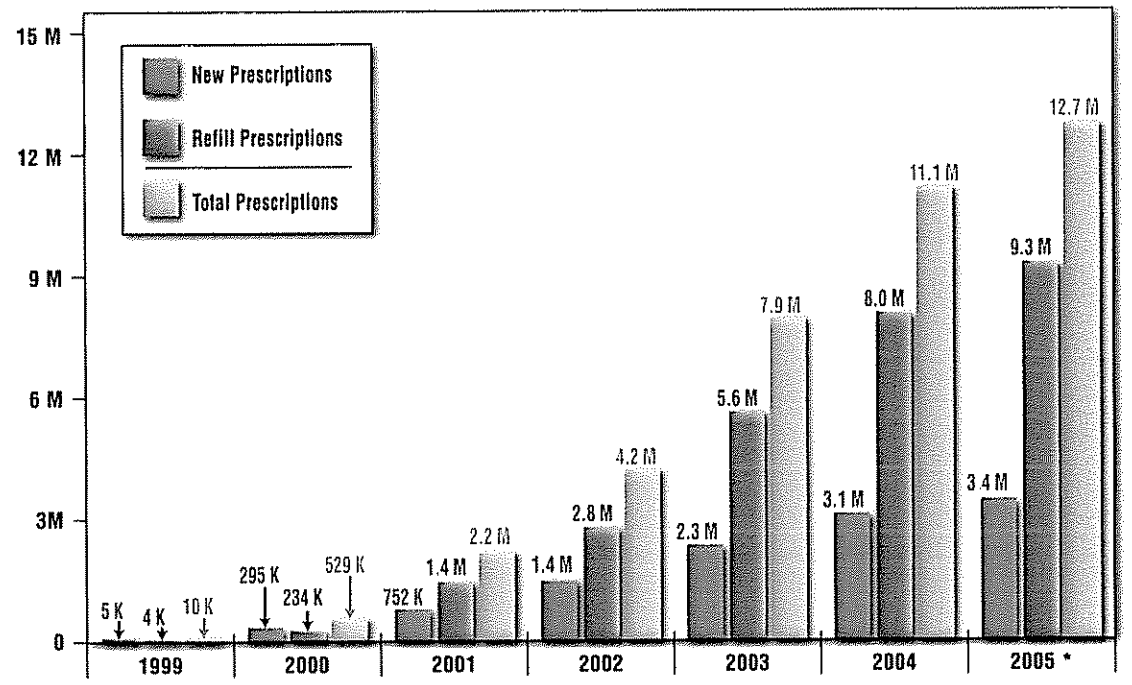
512. That is particularly true here, where the available evidence indicates that P&G's marketing spending on Actonel was less than or comparable to that of its more established competitors during launch. (Tr. at 978:3-980:8 (Smith Dir.); DTX 132 at PGK13663-13664).

513. Published research indicates that the primary reason a new product achieves success is that it serves an unmet need in the market better than other available options. (Tr. at 972:22-14 (Smith Dir.)). In the case of pharmaceuticals, at least one study, by the well-regarded consulting firm McKinsey, has concluded that drugs that are late entrants to the market can achieve "blockbuster" status if they are unique in just one important attribute, such as efficacy or side effect profile. (Tr. at 972:15-973:6 (Smith Dir.); PTX 323).

514. In the case of Actonel, market research reports demonstrate that, based on their prescribing experiences, physicians believe that Actonel delivers the same or comparable efficacy as existing products, (primarily Fosamax), but with a noticeably better side effect profile, particularly with respect to gastrointestinal tolerability. (Tr. at 973:21-975:10 (Smith Dir.); DTX 132 at PGK 13643) ("Perception of superior efficacy (or at a minimum, equivalent efficacy) with improved tolerability vis a vis Fosamax"); Tr. at 385:3-386:9 (Bilezikian Dir.)). In other words, Actonel is believed to have a better therapeutic index, or safety margin, than other existing products, which was the primary objective of the invention of the '122 patent. (JTX 1, col. 11:4-20).

515. Indeed, physician surveys indicate that physicians have a higher overall level of satisfaction with Actonel as compared to its primary competitor, Fosamax. (Tr. at 987:21-990:18 (Smith Dir.); PTX 523 at PG80467). Prescription data supports this observation, showing that prescription refills for Actonel have been steady, and in fact represented about 70% of Actonel's sales by 2005. (Tr. at 984:9-987:20 (Smith Dir.); PTX 319; PTX 320; PTX 321; P-42). Because repeat prescriptions are independent of any marketing, they are particularly compelling evidence that Actonel's success is due to its inherent benefits (and not due to marketing). *(Id).*

516. Slide P-42 depicts new, refill, and total prescriptions of Actonel from 1999 through 2005:



Source: PTX 319; PTX 320; PTX 321 * based on 10 months of data

(Tr. at 986-87 (Smith Dir.); PTX 319; PTX 320; PTX 321).

517. Dr. Lenz admitted that risedronate is a "good drug" and "[i]f it wasn't, we wouldn't be here." (Tr. at 223:17-18 (Lenz Cross)).

1. Teva Offered No Evidence to Rebut P&G's Evidence of Commercial Success

518. Dr. David admitted that he did not dispute that Actonel is a commercial success. (Tr. at 301:15-21 (David Cross)).

519. Dr. David further admitted that he did not dispute that there is a nexus between the claimed benefits of the '122 patent and the commercial success of Actonel. (Tr. at 301:22-302:2 (David Cross)).

520. Dr. David opined that "[f]rom an economic perspective, the commercial success of an invention demonstrates that incentives existed to develop it and bring it to market. The fact that despite these incentives no one did so before the inventor may indicate that the invention was not obvious to those skilled in the art." (Tr. at 326:14-22

(David Cross)). However, Dr. David admitted that he made no effort to determine what incentives existed in the 1980s to develop treatments for osteoporosis. (Tr. at 327:9-14 (David Cross)).

521. Dr. David agreed that the "key issue" in assessing commercial success in the context of patent litigation is whether or not the patented invention earned a positive net return on invested capital. (Tr. at 317:3-9 (David Cross); PTX 533 at 4). However, Dr. David did not analyze whether the patented invention of the '122 patent earned a positive net return on invested capital. (Tr. at 317:11-14 (David Cross)).

522. In Dr. David's opinion, "[p]rofits are proper measure of demand" for a patented invention. (Tr. at 317:15-19 (David Cross); PTX 533 at 6). However, Dr. David did not analyze the profits of Actonel in this case. (Tr. at 318:2-6 (David Cross)).

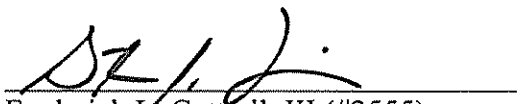
523. Instead, Dr. David testified that he had "addressed the relevance of commercial success" in this case. (Tr. at 301:12-13 (David Cross)).

524. In support of this opinion, Dr. David relied on several assumptions regarding the prior art available to a person of ordinary skill in the art at the time P&G invented risedronate. (Tr. at 297:19-298:2 (David Dir.); Tr. at 328:4-10 (David Cross)). Dr. David did not investigate whether those assumptions were justified. (Tr. at 326:3-8; 328:20-329:4 (David Cross)).

525. Dr. David's opinion regarding the "relevance of commercial success" assumed that the '406 patent, and specifically the 2-pyr EHDP compound, was the relevant prior art at the time risedronate was invented. (Tr. at 298:23-24 (David Dir.); Tr. at 324:22-325:11; 327:20-328:3 (David Cross)).

526. Dr. David's opinion further assumes that P&G was the only entity with knowledge of, or access to, that prior art. (Tr. at 299:1-3 (David Dir.); Tr. at 328:4-10 (David Cross)).

527. Dr. David admitted that if 2 pyr-EHDP was not prior art at the time P&G invented risedronate, he has no opinion. (Tr. at 325:17-21 (David Cross)).



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Dated: December 20, 2006

CERTIFICATE OF SERVICE

I hereby certify that on December 20, 2006, I electronically filed the foregoing document with the Clerk of the Court using CM/ECF which will send notification of such filing(s) and Hand Delivered to the following:

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